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Publiée

Avec rapport de recherche internationale.
Avant l'expiration du délai prévu pour la modification des revendications, sera republiée si de telles modifications sont reçues.

(54) Title: CLADINOSE FOR USE AS A DRUG, AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre: LE CLADINOSE A TITRE DE MEDICAMENT ET LES COMPOSITIONS PHARMACEUTIQUES LE RENFERMANT

(57) Abstract

Cladinose and particularly L-cladinose, for use as a drug, are disclosed. Pharmaceutical compositions containing cladinose and particularly L-cladinose are also disclosed. Cladinose may be used for treating inflammatory conditions in human and animal medicine.

(57) Abrégé

L'invention a pour objet le cladinose et notamment le L-cladinose comme médicament. L'invention a également pour objet les compositions pharmaceutiques renfermant la cladinose et notamment le L-cladinose. Le cladinose peut être utilisé dans le traitement des phénomènes inflammatoires en médecine humaine et animale.

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Le cladinose à titre de médicament et les compositions pharmaceutiques le renfermant.

La présente invention a pour objet le cladinose à titre de médicament et les compositions pharmaceutiques le renfermant.

L'invention a pour objet à titre de médicaments, le cladinose sous toutes ses formes stéréoisomères possibles ainsi que leur mélange.

Le cladinose est un produit connu qui a fait l'objet de différentes publications par E.H. Flynn et Coll. dans J. Am. Chem. Soc., 76, 3121-31 (1954), par P.F. Wiley et Coll. dans J. Am. Chem. Soc., 77, 3422-3 (1955) notamment.

La synthèse du cladinose et du L-cladinose en particulier est décrite par Howarth GB et Coll. dans Can. J. Chem. (1967), 45 (19) 2253-6.

A ce jour, aucune propriété pharmacologique du cladinose n'a été décrite, aucune application thérapeutique n'a été envisagée. On vient de découvrir que le cladinose et notamment le L-cladinose présentait d'intéressantes propriétés pharmacologiques et notamment une intéressante activité anti-inflammatoire qui justifie son utilisation en thérapeutique humaine ou animale.

Les propriétés anti-inflammatoires du cladinose et notamment du L-cladinose ont été déduites d'études in-vitro comparant des macrolides comportant du cladinose et des macrolides ne comportant pas de cladinose.

Des études pharmacologiques réalisées ensuite ont mis en évidence les propriétés anti-inflammatoires du cladinose et notamment du L-cladinose.

Les macrolides à 14 chaînons dérivés de l'érythromycine A possèdent des propriétés anti-inflammatoires.

L'érythromycine A par exemple a été étudiée sur divers modèles expérimentaux d'inflammation par Tarayre J.P. et Coll. 1987 Int. J. Tissue React. 9 : 77-85, par exemple.

Mikasa et Coll. 1992 J. Antimicrob Chemother. 30, 339-347) ont mis en évidence l'activité anti-inflammatoire de l'érythromycine dans le cas de péritonite aseptique chez la

souris.

Tamaoki J. et Coll. (1994 Antimicrob Agents Chemother. 38, 1641-1644), ont mis en évidence l'activité anti-inflammatoire chez le rat, dans le cas d'inflammation trachéale induite par le LPS (ou lipopolysaccharide).

L'activité anti-inflammatoire des macrolides a également été décrite en thérapeutique : chez l'homme, l'érythromycine s'est montrée utile pour le traitement de panbronchiolites diffuses (cf Nagai et Coll, 1991, Respiration 58, 145-149) ou pour le traitement de l'asthme bronchique (cf Miyatake et Coll. 1991, Chest. 99 : 670-673).

Les propriétés anti-inflammatoires de la roxithromycine ont été décrites par C. Agen et Coll. dans Agents Actions 1993, 38 : 85-90 sur des tests classiques d'activité anti-inflammatoire comme le test de l'oedème plantaire aigu à la carraghénine chez le rat, ou le test de l'oedème plantaire aigu à la poly-L-arginine ou l'oedème aigu induit par l'huile de croton.

Il a été décrit que les macrolides et notamment la roxithromycine, la dirithromycine, l'érythromycylanine et l'érythromycine A inhibent in vitro la production d'oxydants par les phagocytes à une étape se situant en amont de la reconstitution de l'enzyme clef des phagocytes, la NADPH oxydase.

Ces propriétés d'inhibition de la production d'oxydants par les phagocytes ont été décrites par exemple par MT Labro et Coll. dans Journal of Antimicrobial Chemotherapy 1993 31, Suppl. C. 51-64 ou Journal of Antimicrobial Chemotherapy 1989, 24, 561-572, ou 1992, 30 509-523.

On a observé également que les macrolides induisaient la dégranulation de polynucléaires neutrophiles humains (PN) in vitro de manière indépendante de leur accumulation cellulaire (cf à ce sujet les articles de Abdelghaffar H. et Coll. Antimicrob. Agents Chemother 1994, 38 : 1548-1554, Labro M.T. et Coll. Program and Abstr. of the 33d Intersci. Conf. Antimicrob. Agent Chemother 1993, abstr. 309).

Les structures chimiques de macrolides induisant à la fois la dégranulation et inhibant la production d'oxydants

(azithromycine, clarithromycine, dirithromycine, érythromycylamine, roxithromycine) ont un point commun : la présence d'un cladinose en 3.

Des études portant sur des macrolides connus qui ne comportent pas de cladinose comme la roxithromycine descladinosylée ou la clarithromycine descladinosylée ont clairement montré que ces molécules se comportaient différemment des molécules comportant un cladinose, comme le montrent les résultats de tests exposés ci-après dans la partie expérimentale.

L'invention a donc pour objet le cladinose et notamment le L-cladinose à titre de médicament.

Le cladinose et notamment le L-cladinose présentent d'intéressantes propriétés anti-inflammatoires qui permettent leur utilisation notamment dans le traitement des algies musculaires, articulaires ou nerveuses, de l'asthme, des affections rhumatismales, des douleurs dentaires et des inflammations de la peau.

L'invention a donc également pour objet le cladinose et notamment le L-cladinose à titre de médicament anti-inflammatoire.

La posologie utile s'échelonne entre 10 et 300 mg par jour chez l'adulte en fonction de la voie d'administration et de l'affection traitée.

L'invention a également pour objet les compositions pharmaceutiques renfermant comme principe actif au moins un des médicaments définis ci-dessus.

Ces compositions peuvent être administrées par voie, buccale, rectale, parentérale ou par voie locale en application topique sur la peau et les muqueuses.

Elles peuvent être solides ou liquides et se présenter sous les formes pharmaceutiques couramment utilisées en médecine humaine, comme par exemple, les comprimés simples ou dragéifiés, les gélules, les granulés, les suppositoires, les préparations injectables, les pommades, les crèmes, les gels ; elles sont préparées selon les méthodes usuelles. Le ou les principes actifs peuvent y être incorporés à des excipients habituellement employés dans ces compositions

pharmaceutiques, tels que le talc, la gomme arabique, le lactose, l'amidon, le stéarate de magnésium, le beurre de cacao, les véhicules aqueux ou non, les corps gras d'origine animale ou végétale, les dérivés paraffiniques, les glycols, les divers agents mouillants, dispersants ou émulsifiants, les conservateurs.

Ces compositions peuvent également se présenter sous forme d'une poudre destinée à être dissoute extemporanément dans un véhicule approprié, par exemple de l'eau stérile apyrogène.

Exemple :

Le L-cladinose a été préparé en suivant par exemple le mode opératoire décrit par Howarth GB et Coll. dans Can. J. Chem. (1967) 45 (19) 2253-6.

I - Exemple de comprimés :

On a préparé des comprimés renfermant :

L-cladinose	150 mg
Excipient qsp	1 g

détail de l'excipient : amidon, talc, stéarate de magnésium.

II - Etude de la production d'O_2^- par les polynucléaires neutrophiles humains stimulés (PMA) en présence de macrolides (100 mg/l).

Le protocole du test utilisé est décrit par MT Labro et Coll. dans Journal of Anti microbial Chemotherapy (1989) 24, 561-572.

Description du test :

Le métabolisme oxydatif des polynucléaires neutrophiles (PN) est étudié par la technique de réduction du cytochrome C, inhibable par la superoxyde dismutase (SOD), décrite par Cohen H.J. et Chovaniec M.E. J. Clin. Invest. 1978, 61 : 1081-1087. Cette technique spectrophotométrique permet de suivre en cinétique la réduction du cytochrome C par l'O_2^- produit par les polynucléaires neutrophiles stimulés par du PMA (100 mg/ml - phorbol myristate acétate) ou un autre stimulant. Les résultats sont exprimés en nmoles d'O_2^- produit par 10^6PN/min. Dans les tests portant sur les substances analysées (macrolides avec et sans cladinose), les PN sont préalablement incubés dans un milieu contrôle (tampon de

dilution) ou en présence de macrolides, pendant 5, 30 ou 60 minutes.

Les résultats obtenus sont les suivants :

Tableau 1 :
Production d'O_2^- par les PN stimulés (PMA)
en présence de macrolides (100 mg/l)

	Temps d'incubation	
	30 minutes	60 minutes
Contrôle : Vi nmole/10^6PN/min		
= 100>	4 ± 1.7 (4 exp.) moyenne ± SEM	4 ± 1.4
% de la réponse contrôle en présence de macrolides		
Roxithromycine	0.6 ± 0.6 (4 exp.)	0 ± 0.0
Roxithromycine sans cladinose	84 ± 14.7 (4)*	76 ± 3.9 (4)*
Clarithromycine	49 ± 18.2 (3 exp.)	24 ± 8.8 (4)
Clarithromycine	92 ± 10.0 (3 exp.)*	69 ± 4.2 (4)

III - Etude de la dégranulation induite par les macrolides

L'étude a été faite selon le protocole du test décrit par H. Abdelgheffar et Coll. dans Anti microbial. Agents and Chemotherapy 1994, 38, 7 : 1548-1554.

Le protocole est le suivant : Dégranulation

Les polynucléaires neutrophiles (PN) incubés (5 à 180 min.) dans un milieu contrôle (tampon de dilution) ou en présence de macrolides, sont centrifugés. Les activités enzymatiques sont mesurées dans le culot cellulaire et le surnageant, et la dégranulation induite est exprimée par le % d'activité enzymatique dans le surnageant sur la somme (culot + surnageant).

Les dosages enzymatiques sont effectués d'après les techniques classiques décrites par Talalay et Coll. 1946, J.

Biol. Chem. 166, 756-772 pour la β-glucuronidase et par Litwack G. 1955 Proc. Soc. Exp. Biol. Med. 89 : 401-403 pour le lysozyme.

Les résultats sont les suivants :

Tableau 2 :
Dégranulation induite par les macrolides

	Temps d'incubation 60 minutes	180 minutes
Enzyme : β-glucuronidase		
Contrôle : dégranulation spontanée	12 ± 1.6 (4 exp.) moyenne ± SEM	16 ± 2.3 (4 exp.)
Roxithromycine	43 ± 3.7 (4 exp.)*	56 ± 2.3 (4)*
Roxithromycine descladinose	15 ± 3.1 (4)**	24 ± 2.4 (4)
Clarithromycine	45 ± 3.0 (3)*	60 ± 6.1 (2)
Clarithromycine descladinose	18 ± 2.1 (3)**	26 ± 9.6 (2)
Lysozyme		
Contrôle :	15 ± 2.0 (4)	19 ± 2.7 (4)
Roxithromycine	39 ± 1.4 (4)*	47 ± 4.6 (4)*
Roxithromycine descladinose	16 ± 2.3 (4)**	24 ± 3.1 (4)**
Clarithromycine	40 ± 2.7 (3)*	55 ± 1.4 (2)
Clarithromycine descladinose	21 ± 4.9 (3)**	26 ± 4.6 (2)

* $p < 0.05$ versus contrôle

** $p < 0.05$ versus la molécule mère

De ces deux tableaux de résultats, on peut déduire que le L-cladinose est responsable en totalité ou en partie des propriétés anti-inflammatoires des macrolides.

Ces propriétés anti-inflammatoires ont ensuite été mises en évidence sur des tests classiques d'activité anti-inflammatoires décrits dans la littérature comme le test de l'oedème plantaire aigu à la carraghénine chez le rat, le test de l'oedème plantaire aigu à la poly-L-arginine ou encore le test de l'oedème aigu induit par l'huile de croton. (Les protocoles utilisés figurent notamment dans l'article de C. Agen et Coll. Agents Actions 38, 1993, p. 85-90).

Les résultats obtenus sur ces tests confirment l'activité anti-inflammatoire du L-cladinose.

REVENDICATIONS

1) A titre de médicament, le cladinose sous toutes ses formes stéréoisomères possibles ainsi que leur mélange.

2) A titre de médicament le L-cladinose.

3) A titre de médicament anti-inflammatoire le cladinose et notamment le L-cladinose.

4) Les compositions pharmaceutiques renfermant comme principe actif au moins un médicament selon l'une quelconque des revendications 1 à 3.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]96/00943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 388 314 (OREAL) 19 September 1990 see the whole document * specially page 4, line 11 to 15 *	1-4
A	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 31, no. c, 1993, pages 51-64, XP000566023 LABRO, M.T. ET AL: "Modulation of human polymorphonuclear neutrophil function by macrolides: preliminary data concerning dirithromycin" cited in the application see the whole document	1-4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 December 1996	11.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 96/00943

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0388314	19-09-90	FR-A- 2644459	21-09-90
		CA-A- 2012218	16-09-90
		DE-D- 69008762	16-06-94
		DE-T- 69008762	25-08-94
		ES-T- 2052201	01-07-94
		JP-A- 2268193	01-11-90
		US-A- 5096713	17-03-92

RAPPORT DE [redacted]HERCHE INTERNATIONALE

D[redacted]ande Internationale No
PCT/[redacted]6/00943

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 A61K31/70

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	EP,A,0 388 314 (OREAL) 19 Septembre 1990 voir le document en entier * surtout page 4, ligne 11 à 15 * ---	1-4
A	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 31, no. c, 1993, pages 51-64, XP000566023 LABRO, M.T. ET AL: "Modulation of human polymorphonuclear neutrophil function by macrolides: preliminary data concerning dirithromycin" cité dans la demande voir le document en entier -----	1-4

☐ Voir la suite du cadre C pour la fin de la liste des documents

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Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
4 Décembre 1996	11. 12. 96

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Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No
PCT/FR 96/00943

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
EP-A-0388314	19-09-90	FR-A-	2644459	21-09-90
		CA-A-	2012218	16-09-90
		DE-D-	69008762	16-06-94
		DE-T-	69008762	25-08-94
		ES-T-	2052201	01-07-94
		JP-A-	2268193	01-11-90
		US-A-	5096713	17-03-92

Example 20

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is cyclo-C_3H_5, R^2 is CH_3

A solution of a sample of Example 1 (150mg, 0.200 mmol) in methanol (5 mL) at room temperature under N_2 was treated sequentially with acetic acid (114 µL, 2.00 mmol), [(1-ethyoxycyclopropyl)oxy]trimethylsilane (200 µL, 1.00 mmol), and $NaBH_3CN$ (63 mg, 1.00 mmol), stirred at room temperature for two hours, heated to reflux for 12 hours, diluted with ethyl acetate (30 mL), washed sequentially with 5% Na_2CO_3 and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel with a gradient of 2% methanol in methylene chloride to 5% methanol in methylene chloride containing 1% ammonium hydroxide to provide 54.4 mg of the desired compound as a white solid. MS (ESI(+)) 792 $(M+H)^+$. HRMS (ESI(+)) m/z calcd for $C_{44}H_{61}N_3O_{10}$: 814.4249 $(M+Na)^+$. Found 814.4243.

Example 21

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(3-pyridyl), R^2 is CH_3

A solution of a sample of Example 1 in methanol (5 mL) at 0 °C under N_2 was treated sequentially with acetic acid (114 µL, 2.00 mmol), 3-pyridinecarboxaldehyde (94 µL, 1.00 mmol) , and sodium cyanoborohydride (63 mg 1.00 mmol), warmed to room temperature with stirring over 18 hours, diluted with ethyl acetate (30 mL), washed sequentially with 5% Na_2CO_3, 2% tris(hydroxymethyl)aminomethane, and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel with 5% methanol in methylene chloride containing 1% ammonium hydroxide to provide 132 mg (78%) of the desired compound as an off-white foam.

MS (APCI) 843 (M+H)+.

HRMS (ESI(+)) m/z calcd for $C_{47}H_{63}N_4O_{10}$: 843.4544 $(M+H)^+$. Found: 843.4562.

Anal. calcd for: C, 66.96; H, 7.41, N, 6.65. Found C, 66.97; H, 7.45; N, 6.57.

Example 22

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(3-hydroxyphenyl), R^2 is CH_3

A solution of a sample of Example 1 (150 mg, 0.200 mmol) in methanol (5 mL) at 0 °C under N_2 was treated with 3-hydroxybenzaldehyde (122 mg, 1.0 mmol), stirred for 5-10 minutes, treated with acetic acid (114 µL, 2.00 mmol), stirred at 0 °C for 10-15 minutes, treated with sodium cyanoborohydride (63 mg, 1.00 mmol), warmed to room temperature over

18 hours, stirred for 48 hours, treated with ethyl acetate (20 mL), washed sequentially with 5% $NaHCO_3$, 2% tris(hydroxymethyl)aminomethane, and brine. If any aqueous extract was too basic (pH 10-12) and contained product, it was treated with NH_4Cl and back-extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel with a gradient of 5% methanol in methylene chloride containing 1% ammonium hydroxide to provide to provide 97.1 mg of the desired compound as a yellow solid.
MS (ESI(+)) m/z 858 $(M+H)^+$.

Example 23

Compound of Formula (II); R is $-CH_2CH=CH-$(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-*tert*-butyl-5-methylphenyl), R^2 is CH_3

A solution of a sample of Example 1 (28 mg, 0.037 mmol) and 3-*tert*-butyl-5-methylphenol (1.5-2.0 equivalents) in toluene (1 mL) in a 1 dram vial was treated with paraformaldehyde (2 equivalents), warmed to 90 °C for 18 hours, and concentrated. If necessary, the vial was uncapped and warmed to permit the toluene to evaporate and drive the reaction to completion. The residue was purified by column chromatography on silica gel with acetone to provide the desired product.
MS (ESI(+)) m/z 928 $(M+H)^+$.

Example 24

Compound of Formula (II); R is $-CH_2CH=CH-$(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3,4-dimethylphenyl), R^2 is CH_3

A sample of Example 1, paraformaldehyde, and 3,4-dimethylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 886 $(M+H)^+$.

Example 25

Compound of Formula (II); R is $-CH_2CH=CH-$(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-(2-propenyl)phenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-allyl-5-methoxyphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 928 $(M+H)^+$.

Example 26

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-methylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-methoxy-5-methylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 902 $(M+H)^+$.

Example 27

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-5-cyclopentylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-cyclopentylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 926 $(M+H)^+$.

Example 28

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-5-carboxamidophenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-hydroxybenzamide were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 901 $(M+H)^+$.

Example 29

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is is CH_2-(2-hydroxy-3-methoxy-5-(2-methoxycarbonylethyl)phenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-(3-hydroxyphenyl)-propionic acid methyl ester were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 944 $(M+H)^+$.

Example 30

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methyl-5-fluorophenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-fluoro-5-methylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 890 $(M+H)^+$.

Example 31

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-acetylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 1-(3-hydroxy-5-methoxy-phenyl)ethanone were processed as described in Example 9 to provide the desired compound.

MS (ESI(+)) m/z 930 $(M+H)^+$.

Example 32

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-bromophenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-bromophenol were processed as described in Example 9 to provide the desired compound.

MS (ESI(+)) m/z 936 $(M+H)^+$.

Example 33

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-alkoxycarbonylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-hydroxy-5-methoxybenzoic acid methyl ester were processed as described in Example 9 to provide the desired compound.

MS (ESI(+)) m/z 946 $(M+H)^+$.

Example 34

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-ethylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-ethylphenol were processed as described in Example 9 to provide the desired compound.

MS (ESI(+)) m/z 886 $(M+H)^+$.

Example 35

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-5-isobutylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-*sec*-butylphenol were processed as described in Example 9 to provide the desired compound.

MS (ESI(+)) m/z 914 $(M+H)^+$.

Example 36

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methyl-5-diethylamino-6-methylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-diethylaminomethyl-2,5-dimethylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 971 $(M+H)^+$.

Example 37

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-4-methyl-5-bromo-6-methylphenyl), R^2 is CH_3

A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-bromo-2,4-dimethylphenol were processed as described in Example 9 to provide the desired compound.
MS (ESI(+)) m/z 964 $(M+H)^+$.

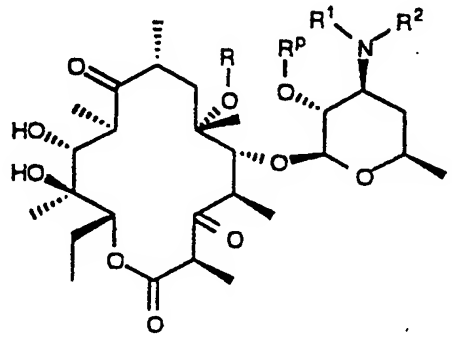
Example 38

Compound of Formula (II): R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-hydroxymethylphenyl), R^2 is CH_3

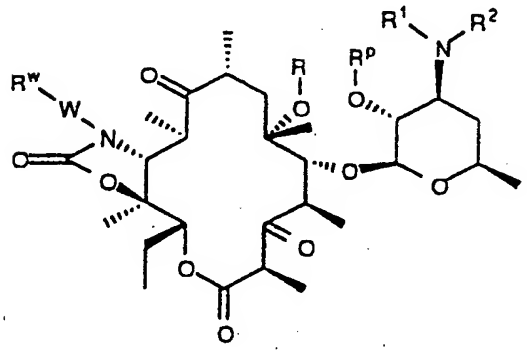
A sample of Example 1 (28 mg, 0.037 mmol), paraformaldehyde, and 3-hydroxymethylphenol were processed as described in Example 9 to provide the desired compound.

WHAT IS CLAIMED IS:

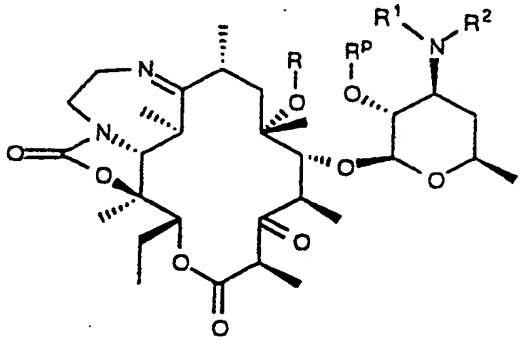
1. A compound selected from the group consisting of



(I)

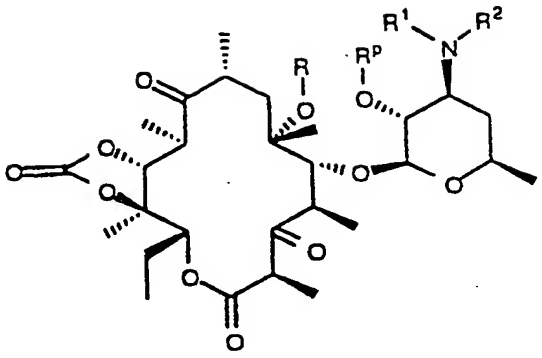


(II)



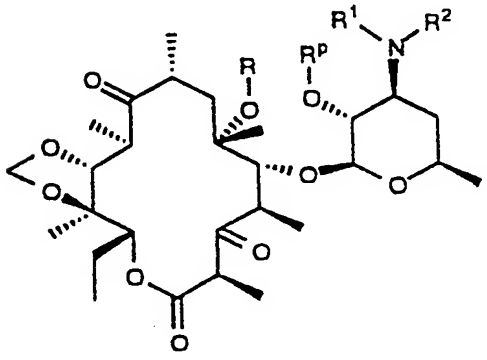
(III)

(IV)



, and

(V)



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein

R^1 and R^2, with the proviso that R^1 and R^2 are not both methyl, are independently selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) C_3-C_6-cycloalkyl,

(c) aryl,

(d) substituted aryl,

(e) heteroaryl,

(f) substituted heteroaryl,

(g) -CHO,

(h) -C(O)-C_1-C_6-alkyl, and

(i) -C(O)-NR'R", wherein R' and R" are independently selected from the group consisting of hydrogen, C_1-C_3-alkyl, C_1-C_3-alkyl substituted with aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

(3) C_2-C_6-alkyl optionally substituted with a substituent selected from the group consisting of
  (a) C_1-C_6-alkoxy,
  (b) -NR'R", wherein R' and R" are as previously defined,
  (c) -NH-C(O)-C_1-C_6-alkyl,
  (d) -NH-C(O)-O-C_1-C_6-alkyl,
  (e) -O-C(O)-O-C_1-C_6-alkyl,
  (f) -O-C(O)-C_1-C_6-alkyl,
  (g) -CH(=N-O-C_1-C_6-alkyl),
  (h) -C(=N-O-C_1-C_6-alkyl)-C_1-C_6-alkyl,
  (i) -CH(=N-NH-C_1-C_6-alkyl), and
  (j) -C(=N-NH-C_1-C_6-alkyl)-C_1-C_6-alkyl,

(4) C_3-C_6-alkenyl optionally substituted with a substituent selected from the group consisting of
  (a) halogen,
  (b) C_3-C_6-cycloalkyl,
  (c) aryl,
  (d) substituted aryl,
  (e) heteroaryl,
  (f) substituted heteroaryl,
  (g) -NH-C(O)-C_1-C_6-alkyl,
  (h) -NH-C(O)-O-C_1-C_6-alkyl,
  (i) -O-C(O)-O-C_1-C_6-alkyl,
  (j) -O-C(O)-C_1-C_6-alkyl,
  (k) -CHO,
  (l) -C(O)-C_1-C_6-alkyl,
  (m) -C(O)-NR'R", wherein R' and R" are as previously defined,
  (n) -CH(=N-O-C_1-C_6-alkyl),
  (o) -C(=N-O-C_1-C_6-alkyl)-C_1-C_6-alkyl,
  (p) -CH(=N-NH-C_1-C_6-alkyl),
  (q) -C(=N-NH-C_1-C_6-alkyl)-C_1-C_6-alkyl, and
  (r) -C(O)-O-C_1-C_6-alkyl,

(5) C_3-C_6-alkynyl optionally substituted with a substituent selected from the group consisting of
  (a) halogen,
  (b) C_3-C_6-cycloalkyl,
  (c) aryl,

(d) substituted aryl,
(e) heteroaryl, and
(f) substituted heteroaryl,

(6) C_3-C_6-cycloalkyl,

(7) -CHO,

(8) -C(O)-C_1-C_6-alkyl,

(9) -C(O)-NR'R", wherein R' and R" are as previously defined, and

(10) -C(O)-O-C_1-C_6-alkyl,

or R^1 and R^2 taken together may be $-(CH_2)_p-$, wherein p is 3-to-7, which taken together with the nitrogen atom to which they are attached, thus form a heterocyclic ring containing one nitrogen atom and from 3 to 7 carbon atoms;

R is selected from the group consisting of

(1) methyl substituted with a substituent selected from the group consisting of
(a) -CN,
(b) -F,
(c) $-CO_2R^3$ wherein R^3 is C_1-C_3-alkyl, aryl-substituted C_1-C_3-alkyl, or heteroaryl-substituted C_1-C_3-alkyl,
(d) $-S(O)_n-R^3$ wherein n is 0, 1, or 2, and R^3 is as previously defined,
(e) -NH-C(O)-R^3 where R^3 is as previously defined,
(f) -NH-C(O)-NR^4R^5 wherein R^4 and R^5 are independently selected from the group consisting of
(i) hydrogen,
(ii) C_1-C_3-alkyl,
(iii) C_1-C_3-alkyl substituted with aryl,
(iv) C_1-C_3-alkyl substituted with substituted aryl,
(v) C_1-C_3-alkyl substituted with heteroaryl, and
(vi) C_1-C_3-alkyl substituted with and substituted heteroaryl,
(g) aryl,
(h) substituted aryl,
(i) heteroaryl,
and
(j) substituted heteroaryl,

(2) C_2-C_{10}-alkyl,

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of
(a) halogen,

(b) hydroxy,
(c) C_1-C_3-alkoxy,
(d) C_1-C_3-alkoxy-C_1-C_3-alkoxy,
(e) oxo,
(f) $-N_3$,
(g) -CHO,
(h) $-O-SO_2$-(substituted C_1-C_6-alkyl),
(i) $-NR^6R^7$ wherein R^6 and R^7 are selected from the group consisting of
(i) hydrogen,
(ii) C_1-C_{12}-alkyl,
(iii) substituted C_1-C_{12}-alkyl,
(iv) C_1-C_{12}-alkenyl,
(v) substituted C_1-C_{12}-alkenyl,
(vi) C_1-C_{12}-alkynyl,
(vii) substituted C_1-C_{12}-alkynyl,
(viii) aryl,
(ix) C_3-C_8-cycloalkyl,
(x) substituted C_3-C_8-cycloalkyl,
(xi) substituted aryl,
(xii) heterocycloalkyl,
(xiii) substituted heterocycloalkyl,
(xiv) C_1-C_{12}-alkyl substituted with aryl,
(xv) C_1-C_{12}-alkyl substituted with substituted aryl,
(xvi) C_1-C_{12}-alkyl substituted with heterocycloalkyl,
(xvii) C_1-C_{12}-alkyl substituted with substituted heterocycloalkyl,
(xviii) C_1-C_{12}-alkyl substituted with C_3-C_8-cycloalkyl,
(xix) C_1-C_{12}-alkyl substituted with substituted C_3-C_8-cycloalkyl,
(xx) heteroaryl,
(xxi) substituted heteroaryl,
(xxii) C_1-C_{12}-alkyl substituted with heteroaryl,
and
(xxiii) C_1-C_{12}-alkyl substituted with substituted heteroaryl,
or
R^6 and R^7 are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which may be substituted with one or more substituents independently selected from the group

consisting of

(i) halogen,

(ii) hydroxy,

(iii) C_1-C_3-alkoxy,

(iv) C_1-C_3-alkoxy-C_1-C_3-alkoxy,

(v) oxo,

(vi) C_1-C_3-alkyl,

(vii) halo-C_1-C_3-alkyl,

and

(vii) C_1-C_3-alkoxy-C_1-C_3-alkyl,

(j) $-CO_2R^3$ wherein R^3 is as previously defined,

(k) $-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(l) $=N-O-R^3$ wherein R^3 is as previously defined,

(m) $-C\equiv N$,

(n) $-O-S(O)_n-R^3$ wherein n and R^3 are as previously defined,

(o) aryl,

(p) substituted aryl,

(q) heteroaryl,

(r) substituted heteroaryl,

(s) C_3-C_8-cycloalkyl,

(t) substituted C_3-C_8-cycloalkyl,

(u) C_1-C_{12}-alkyl substituted with heteroaryl,

(v) heterocycloalkyl,

(w) substituted heterocycloalkyl,

(x) $-NH-C(O)-R^3$ where R^3 is as previously defined,

(y) $-NH-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(z) $=N-NR^6R^7$ wherein R^6 and R^7 are as previously defined,

(aa) $=N-R^3$ wherein R^3 is as previously defined,

(bb) $=N-NH-C(O)-R^4$ wherein R^4 is as previously defined,

and

(cc) $=N-NH-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(4) C_3-alkenyl substituted with a moiety selected from the group consisting of

(a) halogen,

(b) -CHO,

(c) $-CO_2R^3$ where R^3 is as previously defined,

(d) $-C(O)-R^4$ where R^4 is as previously defined,

(e) $-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(f) -C≡N,
(g) aryl,
(h) substituted aryl,
(i) heteroaryl,
(j) substituted heteroaryl,
(k) C_3-C_7-cycloalkyl,
and
(l) C_1-C_{12}-alkyl substituted with heteroaryl,

(5) C_4-C_{10}-alkenyl,

(6) C_4-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of
(a) halogen,
(b) C_1-C_3-alkoxy,
(c) oxo,
(d) -CHO,
(e) $-CO_2R^3$ where R^3 is as previously defined,
(f) $-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,
(g) $-NR^6R^7$ wherein R^6 and R^7 are as previously defined,
(h) $=N-O-R^3$ wherein R^3 is as previously defined,
(i) -C≡N,
(j) $-O-S(O)_n-R^3$ wherein n is 0, 1, or 2 and R^3 is as previously defined,
(k) aryl,
(l) substituted aryl,
(m) heteroaryl,
(n) substituted heteroaryl,
(o) C_3-C_7-cycloalkyl,
(p) C_1-C_{12}-alkyl substituted with heteroaryl,
(q) $-NH-C(O)-R^3$ where R^3 is as previously defined,
(r) $-NH-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,
(s) $=N-NR^6R^7$ wherein R^6 and R^7 are as previously defined,
(t) $=N-R^3$ wherein R^3 is as previously defined,
(u) $=N-NH-C(O)-R^3$ where R^3 is as previously defined,
and
(v) $=N-NH-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(7) C_3-C_{10}-alkynyl,
and

(8) C_3-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl,

and

(e) substituted heteroaryl,

with the proviso that when R is allyl and R^1 is methyl, R^2 is not H;

R^P is hydrogen or a hydroxy protecting group;

R^W is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl, optionally substituted with one or more substituents selected from the group consisting of

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(3) a group selected from option (2) as previously defined further substituted with $-CH_2-M-R^8$, wherein M is selected from the group consisting of

(i) -O-,

(ii) -NH-,

(ii) $-N(CH_3)-$,

(iv) $-S(O)_n-$, wherein n is as described previously,

(v) -NH-C(O)-, and

(vi) -C(O)-NH-,

and

R^8 is selected from the group consisting of

(i) $-(CH_2)_n$-aryl, wherein n is as described previously,

(ii) $-(CH_2)_n$-substituted aryl, wherein n is as described previously,

(iii) $-(CH_2)_n$-heteroaryl, wherein n is as described previously,

(iv) $-(CH_2)_n$-substituted heteroaryl, wherein n is as described previously,

and

(v) $-(CH_2)_n$-heterocycloalkyl, wherein n is as described previously;

and

W is absent or is selected from the group consisting of -O-, -NH- and -N(CH_3)-.

2. A compound according to Claim 1 which is selected from the group consisting of

Compound of Formula (I), R is -CH_2CH=CH-(3-quinolyl), R^p is H, R^1 is methyl, R^2 is hydrogen;

Compound of formula (II), R is -CH_2CH=CH-(3-quinolyl), R^p is acetyl, R^1 is H, R^2 is CH_3, W is absent, R^w is H;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is H, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is acetyl, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is $CH_2C(O)$-O-CH_2CH_3, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2CH=CH_2, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2CH_2F, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-phenyl, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-CN, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-C≡CH, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is $CH_2CH_2CH_3$, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-cyclopropyl, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is cyclopropyl, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(3-pyridyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(cyclo-C_3H_5), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is $CH_2CH_2CH_3$, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent,

R^w is H, R^1 is $CH_2CH=CHC_6H_5$, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is $CH_2C(=CH_2)C(O)OCH_3$, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is $CH_2C(=CH_2)CH_3$, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is cyclo-C_3H_5, R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(3-pyridyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(3-hydroxyphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-*tert*-butyl-5-methylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3,4-dimethylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-(2-propenyl)phenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-methylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-5-cyclopentylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-5-carboxamidophenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is is CH_2-(2-hydroxy-3-methoxy-5-(2-methoxycarbonylethyl)phenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methyl-5-fluorophenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-acetylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-bromophenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^p is H, W is absent, R^w is H, R^1 is CH_2-(2-hydroxy-3-methoxy-5-alkoxycarbonylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^P is H, W is absent, R^W is H, R^1 is CH_2-(2-hydroxy-3-ethylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^P is H, W is absent, R^W is H, R^1 is CH_2-(2-hydroxy-5-isobutylphenyl), R^2 is CH_3;

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^P is H, W is absent, R^W is H, R^1 is CH_2-(2-hydroxy-3-methyl-5-diethylamino-6-methylphenyl), R^2 is CH_3;

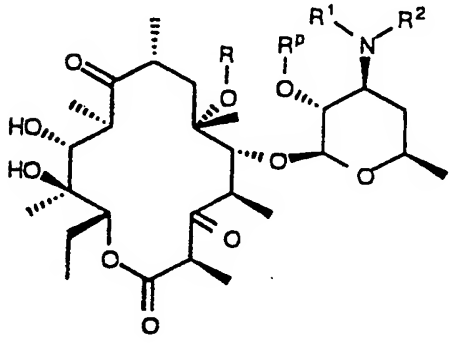
Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^P is H, W is absent, R^W is H, R^1 is CH_2-(2-hydroxy-4-methyl-5-bromo-6-methylphenyl), R^2 is CH_3; and

Compound of Formula (II); R is -CH_2CH=CH-(3-quinolyl), R^P is H, W is absent, R^W is H, R^1 is CH_2-(2-hydroxy-3-hydroxymethylphenyl), R^2 is CH_3.

3. A pharmaceutical composition for treating bacterial infections comprising a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt or ester thereof in combination with a pharmaceutically acceptable carrier.

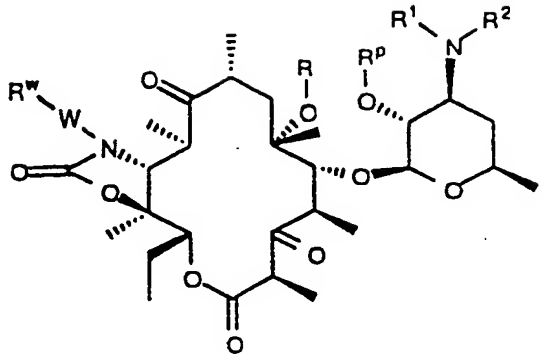
4. A method for treating bacterial infections comprising administering to a mammal in need of such treatment a pharmaceutical composition containing a therapeutically-effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt or ester thereof.

5. A compound according to Claim 1 having the formula (I)



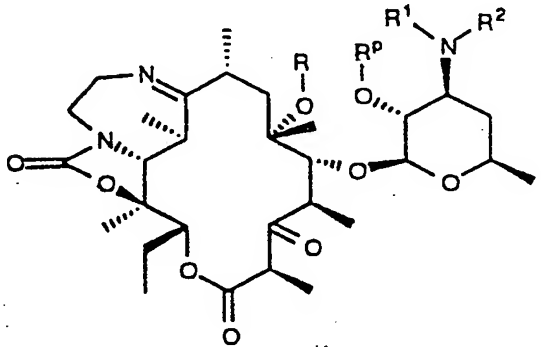
(I)

6. A compound according to Claim 1 having the formula (II)



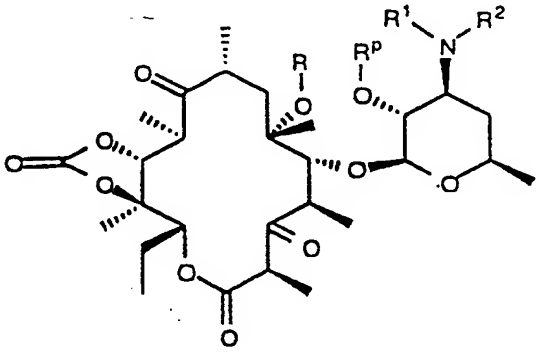
(II)

7. A compound according to Claim 1 having the formula (III)



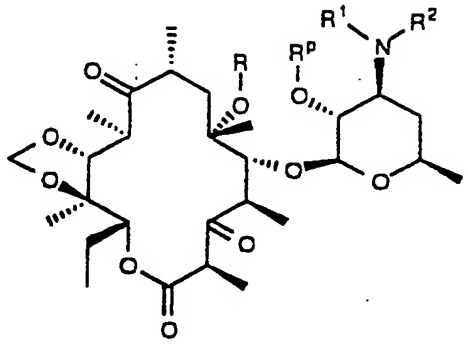
(III)

8. A compound according to Claim 1 having the formula (IV)



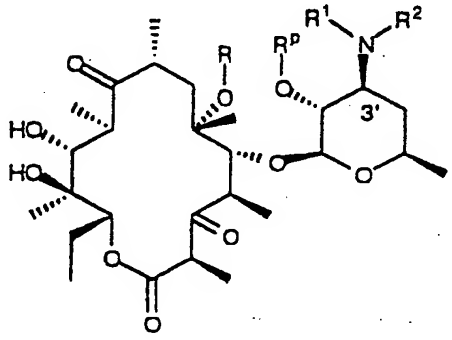
(IV)

9. A compound according to Claim 1 having the formula (V)



(V)

10. A process for preparing a compound selected from the group consisting of



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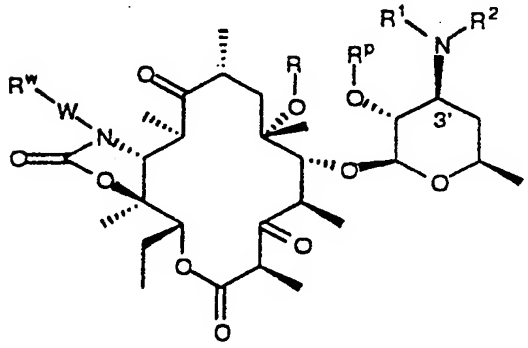
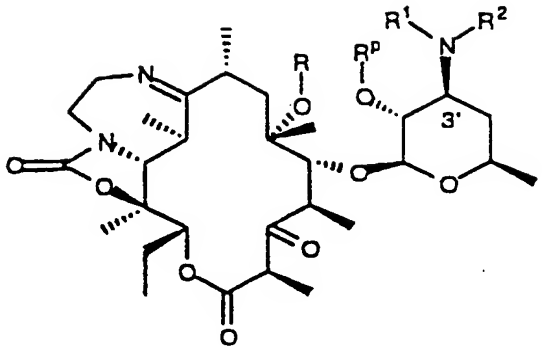
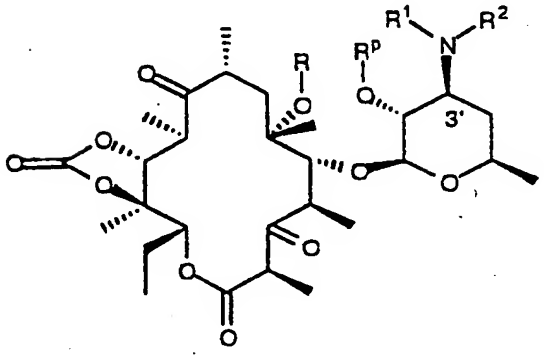


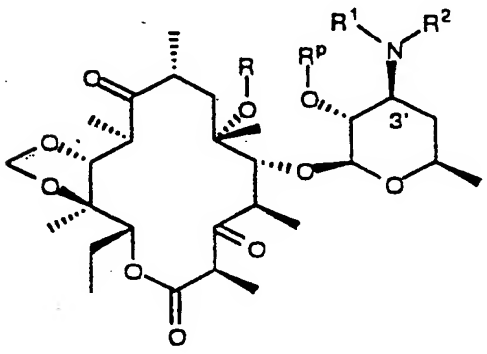
(II),



(III),



(IV), , and



(V),

wherein

R^1 and R^2, with the proviso that R^1 and R^2 are not both methyl, are independently selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) C_3-C_6-cycloalkyl,

(c) aryl,

(d) substituted aryl,

(e) heteroaryl,
(f) substituted heteroaryl,
(g) -CHO,
(h) -C(O)-C_1-C_6-alkyl, and
(i) -C(O)-NR'R", wherein R' and R" are independently selected from the group consisting of hydrogen, C_1-C_3-alkyl, C_1-C_3-alkyl substituted with aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

(3) C_2-C_6-alkyl optionally substituted with a substituent selected from the group consisting of
(a) C_1-C_6-alkoxy,
(b) -NR'R", wherein R' and R" are as previously defined,
(c) -NH-C(O)-C_1-C_6-alkyl,
(d) -NH-C(O)-O-C_1-C_6-alkyl,
(e) -O-C(O)-O-C_1-C_6-alkyl,
(f) -O-C(O)-C_1-C_6-alkyl,
(g) -CH(=N-O-C_1-C_6-alkyl),
(h) -C(=N-O-C_1-C_6-alkyl)-C_1-C_6-alkyl,
(i) -CH(=N-NH-C_1-C_6-alkyl), and
(j) -C(=N-NH-C_1-C_6-alkyl)-C_1-C_6-alkyl,

(4) C_3-C_6-alkenyl optionally substituted with a substituent selected from the group consisting of
(a) halogen,
(b) C_3-C_6-cycloalkyl,
(c) aryl,
(d) substituted aryl,
(e) heteroaryl,
(f) substituted heteroaryl,
(g) -NH-C(O)-C_1-C_6-alkyl,
(h) -NH-C(O)-O-C_1-C_6-alkyl,
(i) -O-C(O)-O-C_1-C_6-alkyl,
(j) -O-C(O)-C_1-C_6-alkyl,
(k) -CHO,
(l) -C(O)-C_1-C_6-alkyl,
(m) -C(O)-NR'R", wherein R' and R" are as previously defined,
(n) -CH(=N-O-C_1-C_6-alkyl),
(o) -C(=N-O-C_1-C_6-alkyl)-C_1-C_6-alkyl,
(p) -CH(=N-NH-C_1-C_6-alkyl),

(q) -C(=N-NH-C_1-C_6-alkyl)-C_1-C_6-alkyl, and

(r) -C(O)-O-C_1-C_6-alkyl,

(5) C_3-C_6-alkynyl optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) C_3-C_6-cycloalkyl,

(c) aryl,

(d) substituted aryl,

(e) heteroaryl, and

(f) substituted heteroaryl,

(6) C_3-C_6-cycloalkyl,

(7) -CHO,

(8) -C(O)-C_1-C_6-alkyl,

(9) -C(O)-NR'R", wherein R' and R" are as previously defined, and

(10) -C(O)-O-C_1-C_6-alkyl,

or R^1 and R^2 taken together may be -$(CH_2)_p$-, wherein p is 3-to-7, which taken together with the nitrogen atom to which they are attached, thus form a heterocyclic ring containing one nitrogen atom and from 3 to 7 carbon atoms;

R is selected from the group consisting of

(1) methyl substituted with a substituent selected from the group consisting of

(a) -CN,

(b) -F,

(c) -CO_2R^3 wherein R^3 is C_1-C_3-alkyl, aryl-substituted C_1-C_3-alkyl, or heteroaryl-substituted C_1-C_3-alkyl,

(d) -$S(O)_n$-R^3 wherein n is 0, 1, or 2, and R^3 is as previously defined,

(e) -NH-C(O)-R^3 where R^3 is as previously defined,

(f) -NH-C(O)-NR^4R^5 wherein R^4 and R^5 are independently selected from the group consisting of

(i) hydrogen,

(ii) C_1-C_3-alkyl,

(iii) C_1-C_3-alkyl substituted with aryl,

(iv) C_1-C_3-alkyl substituted with substituted aryl,

(v) C_1-C_3-alkyl substituted with heteroaryl, and

(vi) C_1-C_3-alkyl substituted with and substituted heteroaryl,

(g) aryl,

(h) substituted aryl,

(i) heteroaryl,

and

(j) substituted heteroaryl,

(2) C_2-C_{10}-alkyl,

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) C_1-C_3-alkoxy-C_1-C_3-alkoxy,

(e) oxo,

(f) $-N_3$,

(g) -CHO,

(h) $-O-SO_2-$(substituted C_1-C_6-alkyl),

(i) $-NR^6R^7$ wherein R^6 and R^7 are selected from the group consisting of

(i) hydrogen,

(ii) C_1-C_{12}-alkyl,

(iii) substituted C_1-C_{12}-alkyl,

(iv) C_1-C_{12}-alkenyl,

(v) substituted C_1-C_{12}-alkenyl,

(vi) C_1-C_{12}-alkynyl,

(vii) substituted C_1-C_{12}-alkynyl,

(viii) aryl,

(ix) C_3-C_8-cycloalkyl,

(x) substituted C_3-C_8-cycloalkyl,

(xi) substituted aryl,

(xii) heterocycloalkyl,

(xiii) substituted heterocycloalkyl,

(xiv) C_1-C_{12}-alkyl substituted with aryl,

(xv) C_1-C_{12}-alkyl substituted with substituted aryl,

(xvi) C_1-C_{12}-alkyl substituted with heterocycloalkyl,

(xvii) C_1-C_{12}-alkyl substituted with substituted heterocycloalkyl,

(xviii) C_1-C_{12}-alkyl substituted with C_3-C_8-cycloalkyl,

(xix) C_1-C_{12}-alkyl substituted with substituted C_3-C_8-cycloalkyl,

(xx) heteroaryl,

(xxi) substituted heteroaryl,

(xxii) C_1-C_{12}-alkyl substituted with heteroaryl,

and

(xxiii) C_1-C_{12}-alkyl substituted with substituted heteroaryl,

or

R^6 and R^7 are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which may be substituted with one or more substituents independently selected from the group consisting of

(i) halogen,

(ii) hydroxy,

(iii) C_1-C_3-alkoxy,

(iv) C_1-C_3-alkoxy-C_1-C_3-alkoxy,

(v) oxo,

(vi) C_1-C_3-alkyl,

(vii) halo-C_1-C_3-alkyl,

and

(vii) C_1-C_3-alkoxy-C_1-C_3-alkyl,

(j) $-CO_2R^3$ wherein R^3 is as previously defined,

(k) $-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(l) $=N-O-R^3$ wherein R^3 is as previously defined,

(m) $-C\equiv N$,

(n) $-O-S(O)_n-R^3$ wherein n and R^3 are as previously defined,

(o) aryl,

(p) substituted aryl,

(q) heteroaryl,

(r) substituted heteroaryl,

(s) C_3-C_8-cycloalkyl,

(t) substituted C_3-C_8-cycloalkyl,

(u) C_1-C_{12}-alkyl substituted with heteroaryl,

(v) heterocycloalkyl,

(w) substituted heterocycloalkyl,

(x) $-NH-C(O)-R^3$ where R^3 is as previously defined,

(y) $-NH-C(O)-NR^4R^5$ wherein R^4 and R^5 are as previously defined,

(z) $=N-NR^6R^7$ wherein R^6 and R^7 are as previously defined,

(aa) $=N-R^3$ wherein R^3 is as previously defined,

(bb) $=N-NH-C(O)-R^4$ wherein R^4 is as previously defined,

and

(cc) =N-NH-C(O)-NR^4R^5 wherein R^4 and R^5 are as previously defined.

(4) C_3-alkenyl substituted with a moiety selected from the group consisting of

(a) halogen,

(b) -CHO,

(c) -CO_2R^3 where R^3 is as previously defined,

(d) -C(O)-R^4 where R^4 is as previously defined,

(e) -C(O)-NR^4R^5 wherein R^4 and R^5 are as previously defined,

(f) -C≡N,

(g) aryl,

(h) substituted aryl,

(i) heteroaryl,

(j) substituted heteroaryl,

(k) C_3-C_7-cycloalkyl,

and

(l) C_1-C_{12}-alkyl substituted with heteroaryl,

(5) C_4-C_{10}-alkenyl,

(6) C_4-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of

(a) halogen,

(b) C_1-C_3-alkoxy,

(c) oxo,

(d) -CHO,

(e) -CO_2R^3 where R^3 is as previously defined,

(f) -C(O)-NR^4R^5 wherein R^4 and R^5 are as previously defined,

(g) -NR^6R^7 wherein R^6 and R^7 are as previously defined,

(h) =N-O-R^3 wherein R^3 is as previously defined,

(i) -C≡N,

(j) -O-$S(O)_n$-R^3 wherein n is 0, 1, or 2 and R^3 is as previously defined,

(k) aryl,

(l) substituted aryl,

(m) heteroaryl,

(n) substituted heteroaryl,

(o) C_3-C_7-cycloalkyl,

(p) C_1-C_{12}-alkyl substituted with heteroaryl,

(q) -NH-C(O)-R^3 where R^3 is as previously defined,

(r) -NH-C(O)-NR^4R^5 wherein R^4 and R^5 are as previously defined,

(s) =N-NR^{6}R^7 wherein R^6 and R^7 are as previously defined,

(t) =N-R^3 wherein R^3 is as previously defined,

(u) =N-NH-C(O)-R^3 where R^3 is as previously defined,

and

(v) =N-NH-C(O)-NR^{4}R^5 wherein R^4 and R^5 are as previously defined,

(7) C_3-C_{10}-alkynyl,

and

(8) C_3-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl,

and

(e) substituted heteroaryl,

with the proviso that when R is allyl and R^1 is methyl, R^2 is not H;

R^p is hydrogen or a hydroxy protecting group;

R^w is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl, optionally substituted with one or more substituents selected from the group consisting of

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(3) a group selected from option (2) as previously defined further substituted with -CH_2-M-R^8, wherein M is selected from the group consisting of

(i) -O-,

(ii) -NH-,

(ii) -N(CH_3)-,

(iv) -S(O)$_n$-, wherein n is as described previously,

(v) -NH-C(O)-, and

(vi) -C(O)-NH-,

and

R^8 is selected from the group consisting of

(i) $-(CH_2)_n$-aryl, wherein n is as described previously,

(ii) $-(CH_2)_n$-substituted aryl, wherein n is as described previously,

(iii) $-(CH_2)_n$-heteroaryl, wherein n is as described previously,

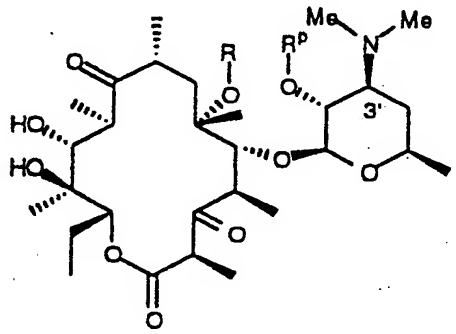
(iv) $-(CH_2)_n$-substituted heteroaryl, wherein n is as described previously, and

(v) $-(CH_2)_n$-heterocycloalkyl, wherein n is as described previously; and

W is absent or is selected from the group consisting of -O-, -NH- and $-N(CH_3)-$,

the method comprising:

(a) sequentially desmethylating 3'-nitrogen of a compound selected from the group consisting of



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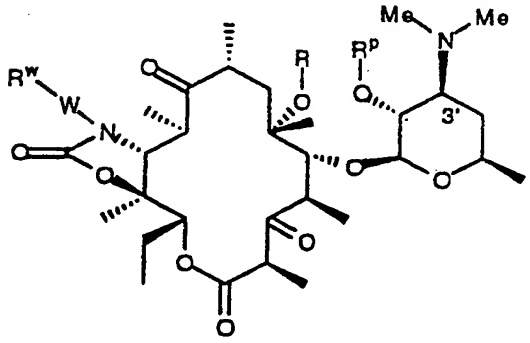

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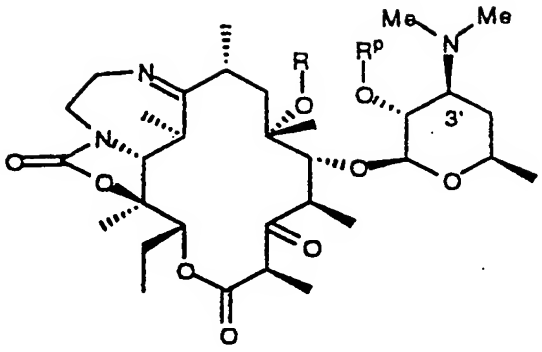
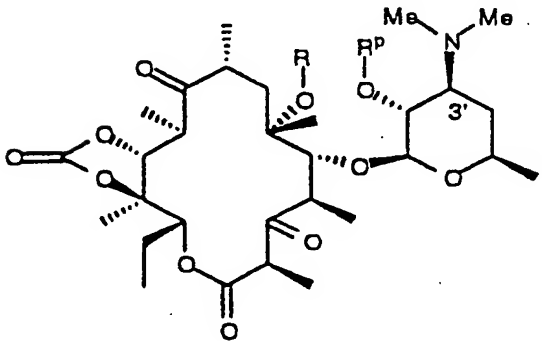
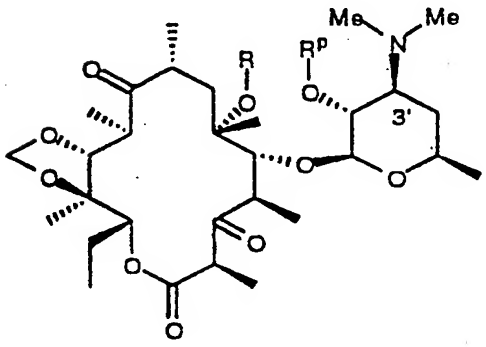
(C), 

(D),  , and

(E),  ,

wherein R, and R^p are as defined previously; and

(b) sequentially reacting the compound from step (a) with a R^1-and a R^2-precursor compound.

11. The process of Claim 10, wherein the desmethylation of the 3'-nitrogen is obtained by reacting the compound with N-iodosuccinimide to afford a corresponding compound having a 3'-$NHCH_3$ group.

12. The process of Claim 11, wherein in step (b), the compound is reacted with a R^1-precursor selected from the group consisting of

(i) R^1-X wherein R^1 is as defined previously and X is a halide or sulfonate leaving group,

(ii) an aldehyde of formula R*-CHO followed by reduction to give R*-CH_2, the R^1 moiety described previously,

(iii) carbonyldiimidazole to give an intermediate compound wherein R^1 is imidazolylcarbonyl and reacting this intermediate with an amine having the formula HNR'R", wherein R' and R" are as defined previously, to give a compound wherein R^1 is C(O)-NR'R",

(iv) an alcohol of the formula HOR', wherein R' is as previously defined. to give a compound wherein R^1 is C(O)-OR',

(v) an acylating agent of the formula X-C(O)-R', wherein X is halogen and R' is as defined previously, or O-(C(O)-R')$_2$ to give a compound wherein R^1 is C(O)R', and

(vi) a substituted or unsubstituted aryl alcohol and a homologating agent selected from formaldehyde or paraformaldehyde to give a compound wherein R^1 is methyl substituted with substituted aryl.

13. The process of Claim 11, further comprising treating the compound with iodosuccinimide or iodine in presence of light to afford a corresponding compound having a 3'-NH_2 group.

14. The process of Claim 13, further comprising treating the compound with a R^1-precursor to afford a compound having a 3'-NHR^1CH_3 group, wherein the R^1-precursor is selected from the group consisting of

(i) R^1-X wherein R^1 is as defined previously and X is a halide or sulfonate leaving group,

(ii) an aldehyde of formula R*-CHO followed by reduction to give R*-CH_2, the R^1 moiety described previously,

(iii) carbonyldiimidazole to give an intermediate compound wherein R^1 is imidazolylcarbonyl and reacting this intermediate with an amine having the formula HNR'R", wherein R' and R" are as defined previously, to give a compound wherein R^1 is C(O)-NR'R",

(iv) an alcohol of the formula HOR', wherein R' is as previously defined, to give a compound wherein R^1 is C(O)-OR',

(v) an acylating agent of the formula X-C(O)-R', wherein X is halogen and R' is as defined previously, or O-(C(O)-R')$_2$ to give a compound wherein R^1

is C(O)R', and

(vi) a substituted or unsubstituted aryl alcohol and a homologating agent selected from formaldehyde or paraformaldehyde to give a compound wherein R^1 is methyl substituted with substituted aryl.

15. The process of Claim 14, further comprising treating the compound with a R^2-precursor compound to afford a compound having a 3'-NR^1R^2 group, wherein the R^2-precursor is selected from the group consisting of

(i) R^2-X wherein R^2 is as defined previously and X is a halide or sulfonate leaving group,

(ii) an aldehyde of formula R*-CHO followed by reduction to give R*-CH_2-, the R^2 moiety described previously,

(iii) carbonyldiimidazole to give an intermediate compound wherein R^2 is imidazolylcarbonyl and reacting this intermediate with an amine having the formula HNR'R", wherein R' and R" are as previously defined, to give a compound wherein R^2 is C(O)-NR'R",

(iv) an alcohol of the formula HOR' to give a compound wherein R^2 is C(O)-OR',

(v) an acylating agent of the formula X-C(O)-R', wherein X is halogen and R' is as defined previously, or O-$(C(O)-R')_2$ to give a compound wherein R^2 is C(O)R', and

(vi) a substituted or unsubstituted aryl alcohol and a homologating agent selected from formaldehyde or paraformaldehyde to give a compound wherein R^1 is methyl substituted with substituted aryl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 98/19311

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17356 A (ABBOTT LAB) 15 May 1997 cited in the application see page 1, line 2 - line 6 see claims 1,13	1,3,10
A	US 5 444 051 A (AGOURIDAS CONSTANTIN ET AL) 22 August 1995 cited in the application see column 1, line 17 - line 26 see column 6, line 29 - line 43 see claims 1,9,10,19	1,3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1999	26/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[redacted]na pplication No
PC[redacted]S 98/19311

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SUWA T ET AL: "UPTAKE OF O-ALKYL ERYTHROMYCIN DERIVATIVES IN THE LUNG TISSUE AND CELLS OF RATS" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 79, no. 9, September 1989, page 783/784 XP002035991 see page 783, left-hand column, last paragraph see page 784, left-hand column, last paragraph	1,3
A	MORIMOO S. ET AL.: "Chemical modifications of erythromycins. II. Synthesis and antibacterial activity of o-alkyl derivatives of erythromycin A" THE JOURNAL OF ANTIBIOTICS, vol. 43, 1990, pages 286-294, XP002093093 cited in the application see page 286, paragraph 1 see page 287, compounds 13 and 14	1,10

INTERNATIONAL SEARCH REPORT

Internat. al application No.
PCT/US 98/19311

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: 3
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]ication No
PC[illegible]S 98/19311

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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